

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19365 A1

(51) International Patent Classification⁷: **A61K 31/195**,
35/78, 7/48 // (A61K 35/78, 31:195)

(21) International Application Number: **PCT/EP00/08742**

(22) International Filing Date:
7 September 2000 (07.09.2000)

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
99118284.1 15 September 1999 (15.09.1999) **EP**

(71) Applicant: **ROCHE CONSUMER HEALTH AG**
[CH/CH]; Wurmisweg, CH-4303 Kaiseraugst (CH).

(72) Inventors: **DE BONY, Raymond**; 31, route du Bois,
CH-1024 Ecublens (CH). **GOORIS, Eric**; 19, chemin du
Grand-Pré, Verrières, F-74160 Neydens (FR).

(74) Agent: **WAECHTER, Dieter**; Grenzacherstrasse 124,
CH-4070 Basle (CH).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ,
VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- *With international search report.*
- *Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: **PHARMACEUTICAL AND/OR COSMETICAL COMPOSITIONS**

(57) Abstract: The present invention relates to pharmaceutical and/or cosmetic compositions comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives. The compositions according to the present invention show an important activity in the neosynthesis of collagens, in contrast to compositions containing separately the same amount of the two active compounds. They are suitable for treating dermatological disorders such as wound-healing, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

WO 01/19365 A1

Pharmaceutical and/or cosmetical compositions

The present invention relates to pharmaceutical and/or cosmetical compositions for treating dermatological disorders such as wound-healing, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

- 5 It is known that compositions containing pantothenic acid and/or its derivatives are useful for healing wounds and for treating further dermatological disorders.

Pantothenic acid, which is also known as D(+) N-(2,4-dihydroxy-3,3-dimethylbutyryl) β -alanine, is a member of the B complex vitamins and is sometimes referred to as vitamin B5.

- 10 Pantothenic acid plays a key role in cellular metabolism, as after incorporation into coenzyme A (CoA), it participates in the synthesis of fatty acids, cholesterol and sterols. Through its participation in the Krebs cycle, coenzyme CoA is also instrumental in the generation of energy by the cells. Pantothenic acid is hence essential for epithelial regeneration and development in the event of damage to the skin when a high rate of lipids and cellular renewal is needed.

- 15 Dexpanthenol, the alcohol of the pantothenic acid, is well absorbed by the skin. After penetration in the skin it is rapidly transformed into pantothenic acid. Dexpanthenol has therefore been used for many years in topical products such as ointments and creams. The clinical effectiveness of the topical application of dexpanthenol in promoting wound healing has been confirmed by several studies in cases of wounds, burns, cracked nipples, 20 ulcers, and bedsores (e.g. P.Girard, A.Béraud, C.Goujon, A.Sirvent, J-L Foyatier, B. Alleaume, R. de Bony, *Les Nouvelles Dermatologiques*, 17, 1998, pp 559-570).

- Centella Asiatica is a plant of the umbelliferae family and has been used for wound healing. Centella Asiatica is also suitable for cosmetic use such as skin conditioning improvement and anti-cellulite effect. Centella Asiatica contains asiatic acid, madecassic acid and 25 asiaticoside, all of which belong to the class of triterpenoids. Titrated Extract of Centella Asiatica (TECA, Serdex) is a combination of 40 wt % asiaticoside and 60 wt % of the two genines asiatic acid and madecassic acid.

5 Titrated Extract of Centella Asiatica is commercially available under the trademark MADECASSOL® or can be prepared by maceration of dried plants of Centella Asiatica and various purification steps. (*International Cosmetic, Ingredient Dictionary*, 5th Edition, 1993, Editors: John A. Wenninger et al, published by The Cosmetic, Toiletry, and Fragrance Association).

Asiatic acid, asiaticoside and madecassic acid are known and commercially available compounds and can be prepared as described in "International Cosmetic, Ingredient Dictionary", 5th Edition 1993, Editors: John A. Wenninger et al, published by The Cosmetic, Toiletry, and Fragrance Association.

10 It has been now surprisingly found that compositions comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives, show an important activity in the neosynthesis of collagens, in contrast to compositions containing separately the same amount of the two
15 active compounds.

The synergetic action of the two compounds tested in association enables therefore to provide therapeutically active pharmaceutical and/or cosmetical compositions with enhanced potency. Compositions with higher therapeutic activity are therefore obtained without enhancing the amount of active compounds and, therefore, without
20 compromising the patient's tolerance of the active principles and without increasing the manufacturing costs.

The compositions according to the present invention can contain asiatic acid, asiaticoside and madecassic acid, singly or in any combination thereof. Preferably, the composition according to the present invention comprises 0.5 to 1.5 wt % of TECA.

25 Any pharmaceutically and/or cosmetically acceptable derivative of pantothenic acid can be used in the compositions of the present invention. Examples include alcohols, aldehydes, alcohol esters, acid esters and the like. The preferred derivative of pantothenic acid is pantothenyl alcohol (panthenol), particularly the D(+) of pantothenyl alcohol which is more commonly known as dexpanthenol. As preferred alcohol ester, pantothenyl triacetate
30 can be chosen.

The composition according to the present invention may further comprise additional vitamins such as vitamin A, vitamins B other than pantothenic acid, vitamin C and vitamin E. Vitamins B other than pantothenic acid, vitamin C and/or vitamin E can be present in an amount varying from 0.01 wt % to 10.0 wt %, while Vitamin A can be suitably used in
35 concentrations from 1000 to 5000 IU per gram of composition.

If used for treating chronic venous insufficiency, the composition according to the present invention may contain active principles for this purpose. Examples thereof are escin, rutosides and mixtures thereof. They can be incorporated into the composition either in pure form or by means of natural extracts containing them. A preferred extract containing
5 escin is that of Horse Chestnut, while preferred extracts containing rutosides are those of Sophora Japonica and Ginkgo Biloba.

According to the present invention, the composition may also contain minerals for supporting the regeneration and maintenance of human tissues such as the skin and/or the blood vessel tissues. Such minerals are preferably selected from those including Se, Zn, Mg
10 and Ca.

The pharmaceutical and/or cosmetical compositions of the present invention can comprise pharmaceutically and/or cosmetically acceptable additives. Suitable additives are diluents, dispersants and carriers of the active compounds. Additives other than water can include liquid and solid emollients, solvents, thickeners, emulsifiers, preservatives, coloring agents,
15 opacifiers, sunscreens, and the like. The additives form the balance of the composition.

Emollients can be chosen from the group consisting of esters, fatty acids and alcohols, polyols, oils and waxes and are preferably present in amounts varying from 0.5 and 60 wt %.

Esters may be mono-, di- or triesters such as glycerylolate, polyethylenglycolstearate, dibutyladipate, diethylsebacate, dioctylsuccinate, triisopropyltrilinoleate or trilaurylcitrate.
20 Esters may also be straight chain fatty acids such as laurylpalmitate, myristyllactate or stearylolate; or branched chain fatty esters such as isopropylstearate or isostearylpalmitate.

Fatty acids and alcohols include those compounds having from 10 to 20-carbon atoms like for example cetyl-, myristyl-, palmitic- and stearyl-alcohols and -acids or lanolin alcohol.

25 Polyols may be linear or branched chain alkyl polyhydroxyl compounds like for example propylene glycol, sorbitol or glycerin or polymeric polyols such as polyethylenglycol (PEG).

Oils may be mineral oils like paraffin oil or vaseline, vegetable oils like almond oil, palm oil, avocado oil, castor oil or olive oil, silicone oils like for example dimethicone.

30 Waxes may be mineral waxes like paraffin wax, white wax, vaseline or ozokerite or animal waxes like woolfat or beeswax.

Solvents are preferably alcohols such as ethanol.

Thickeners will usually be present in amounts from 0.1 wt % to 20 wt %. Exemplary thickeners are gelatin or polyacrylamide.

Preservatives may include phenoxyethanol, paraben-compounds, chlorphenesin, EDTA, benzylic alcohol, benzalkonium chloride and chlorhexidine.

- 5 Sunscreens include, in amounts varying from 0.1 wt % to 20 wt %, those materials commonly employed to block ultraviolet light, such as PARSOL® 1789 or PARSOL® MCX. Physical filters, such as micronized zinc oxide or titan dioxide, may also be included in the compositions of the present invention.

Emulsifiers may be incorporated into the compositions from about 0.1 wt % to 20 wt %.

- 10 Emulsifiers can be nonionic surfactants such as polyalkylene glycol ethers of fatty alcohols, anionic surfactants such as alkyl sulfates, fatty acid soaps, amphoteric surfactants such as dialkylamine oxide.

- The composition according to the present invention is intended primarily as a product for topical application. The term "topical" as used in the present specification relates to the use of the above active compounds, which are processed with a suitable carrier material and which is applied to the skin, mucous membrane, hair and/or nails, so that it can display local activity. Accordingly, the topical forms embrace pharmaceutical and/or cosmetical dosage forms which are suitable for external use, so that a direct contact with the skin results. The topical dosage forms embrace gels, creams, lotions, salves, powders, aerosols, emulsions, including oil in water and water in oil, and other conventional forms which are suitable for the direct application of products on the skin or mucous membrane. These dosage forms can be manufactured by mixing the above compounds with known carrier materials which are suitable for topical use.

- 25 Salves and creams contain oily, absorbent, water-soluble and/or emulsifying carrier materials such as vaseline, paraffin oil, propylene glycol, cetylalcohol, glycerine monostearate, alkyl-branched fatty acids and the like.

- Lotions are liquid preparations and can vary from simple solutions to aqueous or aqueous/alcoholic preparations which contain the substances in finely divided form. The preparations contain suspended or dispersing substances such as, for example, sodium carboxymethylcellulose which suspend or disperse the active substance in a carrier prepared from water, alcohol, glycerine and the like.

Gels are semi-solid preparations which are obtained by gelling a solution or suspension of the active substance in a carrier material. The carrier materials, which can be hydrophilic

or hydrophobic, are gelled using a gelling agent in form of polymers of biological, natural or synthetical origin.

Aerosols are solutions or suspensions of the active substance in a carrier material which are applied using spray generators. Usually used carriers are, for example,

5 trichloromonofluoromethane, trichlorodifluoromethane, volatile silicones, nitrogen, etc..

Spays are solutions suspensions or powders of the active substance in a carrier material which are applied using mechanical pumps.

The compositions according to the present invention are used by applying an amount of the active compounds sufficient to provide a therapeutic and/or cosmetic effect to the skin to be treated. This application can be effected in the usual manner by rubbing, spraying or
10 by a plaster.

The topical compositions are usually applied in an amount to provide from 0.1 to 5 mg of active ingredient per cm² of the skin per day.

The inventive combination can also be administered orally for stimulating collagen synthesis in skin or for the treatment of chronic venous insufficiency and any other
15 diseases originating from collagen deficiency. Oral administrations can be presented, for example, in the form of tablets, capsules, solutions, etc. For oral administration the compositions of the invention can be administered to adults in amounts of about 10-400 mg/day.

20 The present invention refers also to the use of a combination comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives for the manufacture of medicaments and/or
25 cosmetic compositions. Preferably, such medicaments and/or cosmetic compositions are used for treating wounds, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

It is also an object of the present invention to provide a process for preparing the above pharmaceutical and/or cosmetic compositions, comprising mixing from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of
30 Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.

The invention is illustrated in more detail by the following example.

Example: Bepanthen DECA

	Dexpantenol:	5.0g
	Titrated Extract of Centella Asiatica (TECA):	1.0g
	Paraffin Oil:	13.5g
5	Octyl stearate:	12.0g
	Propylene glycol:	5.0g
	Caprylic, capric, isostearic, adipic acids glycerol ester:	5.0g
	Almond oil:	5.0g
	PEG 30 dipolyhydroxystearate:	4.0g
10	PEG 22 dodecyl glycol copolymer:	3.0g
	Glyceryl behenate:	3.0g
	Microcrystalline wax:	2.0g
	Paraffin wax:	1.5g
	Cetostearyl alcohol:	1.0g
15	Pantolactone	0.5g
	Magnesium sulfate:	0.5g
	Phenoxyethanol:	0.3g
	Chlorphenesin:	0.2g
	Citric acid	0.004 g
20	Sodium chloride:	0.2g
	Purified water:	up to 100 g

The above composition was applied to male and female human volunteers between 20 and 45 years on wounds created according to an artificial wound model (biopsies with a 3 mm punch). The wound healing degree was evaluated after 1, 3, 6 and 10 days of treatment, with a scoring of epidermisation and dermis restructuring made on Dermascan[®] echographies. The evaluation of the wound status was carried out by means of video microscopic images taken at different times during the healing period.

Clinical results are shown in table 1, wherein the efficacy of Bepanthen Deca has been compared to that of Bepanthen Ointment (5% dexpantenol) and Madecassol Cream (1% TECA). The results are expressed as wound healing degree, wherein 0.0 and 4.0 represent the lowest value (0% healing) and the highest value (100% healing), respectively.

Tab. 1 Clinical results

Composition	1 Day	3 Days	6 Days	10 Days
Bepanthen Deca	0.0	0.0	0.5	0.9

- 7 -

Bepanthen Ointment	0.0	0.1	0.4	0.6
Madecassol Cream	0.0	0.0	0.1	0.1

As shown in Table 1, a synergetic effect of dexpanthenol and TECA is observed. After 10 days of treatment, the wound healing degree obtained using Bepanthen Deca is higher (0.9) than that which could be obtained by using the two compounds separately (0.6+0.1).

- 5 This unexpected synergy enables the use of low concentrations of active compounds, thereby reducing the patient's intolerance risks and the manufacturing costs of the medicament and/or cosmetical product.

Claims

1. Pharmaceutical and/or cosmetical composition comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.
2. Pharmaceutical and/or cosmetical composition according to claim 1 comprising 0.5 to 1.5 wt % of TECA.
3. Pharmaceutical and/or cosmetical composition according to claim 2, comprising 1 wt % of TECA.
4. Pharmaceutical and/or cosmetical composition according to any preceding claim, comprising from 4 to 6 wt % of dexpanthenol.
5. Pharmaceutical and/or cosmetical composition according to claim 4, comprising 5 wt % of dexpanthenol.
6. Pharmaceutical composition according to any preceding claim, further comprising vitamins selected from the group consisting of vitamin A, vitamins B other than pantotenic acid, vitamin C and vitamin E.
7. Pharmaceutical composition according to any preceding claim, further comprising minerals for supporting the regeneration and maintenance of human tissues.
8. Pharmaceutical and/or cosmetical composition according to any preceding claim, further comprising additives chosen from the group consisting of liquid and solid emollients, solvents, thickeners, emulsifiers, preservatives, coloring agents, opacifiers and sunscreens.
9. Pharmaceutical composition according to any preceding claim, further comprising active compounds for treating chronic venous insufficiency.
10. Pharmaceutical composition according to claim 9, wherein the compound for treating chronic venous insufficiency is chosen from the group consisting of escin, rutosides and mixtures thereof.
11. Use of a combination comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid

and/or its derivatives for the manufacture of medicaments and/or cosmetical compositions.

12. Use according to claim 11 for treating wounds, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.
- 5 13. Process for preparing a pharmaceutical and/or cosmetical composition according to any one of claim 1 to 10, comprising mixing from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.
- 10 14. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Inter. l. onal Application No

PCT/EP 00/08742

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K35/78 A61K7/48 //(A61K35/78,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, EMBASE, CHEM ABS Data, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 852 946 A (PAOLI AMBROSI GIANFRANCO DE) 15 July 1998 (1998-07-15) *cf. abstract, page 3, lines 53 bridging with page 4, first line, and lines 14-18*	1-13
A	FR 2 770 776 A (LVMH RECH) 14 May 1999 (1999-05-14) *cf. page 5, lines 15-36 with page 6, lines 1-11*	1-13
A	FR 2 668 061 A (THOREL JEAN NOEL) 24 April 1992 (1992-04-24) *cf. abstract, page 4 and page 5, lines 1-18*	1-13
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

18 January 2001

Date of mailing of the international search report

05/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Stoltner, A

INTERNATIONAL SEARCH REPORT

Inter. .onal Application No

PCT/EP 00/08742

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03676 A (CABO SOLER JOSE ; CALDERON GOMEZ JESUS (ES); PALACIOS GIL ANTUNANO) 6 February 1997 (1997-02-06) *cf. abstract, page 6, example 1, formulation 6*	1-13
A	US 5 945 109 A (SCHMIDT ALFRED ET AL) 31 August 1999 (1999-08-31) *cf. abstract, col. 1, last para., bridging with col. 2, first para.*	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/08742

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0852946 A	15-07-1998	IT BS960094 A CA 2219849 A US 6147054 A	29-05-1998 29-05-1998 14-11-2000
FR 2770776 A	14-05-1999	EP 1028705 A WO 9924009 A	23-08-2000 20-05-1999
FR 2668061 A	24-04-1992	NONE	
WO 9703676 A	06-02-1997	ES 2098193 A AU 6419696 A	16-04-1997 18-02-1997
US 5945109 A	31-08-1999	AU 1793397 A WO 9736570 A EP 0907351 A	22-10-1997 09-10-1997 14-04-1999